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Do nonsteroidal anti-inflammatory drugs affect the risk of developing ovarian cancer? A meta-analysis

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Aim
The relationship between the use of nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, and the risk of ovarian cancer has been controversial. This study examines the strength of this association by conducting a detailed meta-analysis of the studies published in peer-reviewed literature on the subject.

Methods
A comprehensive search for articles published up to April 2004 was performed, reviews of each study were conducted and data were abstracted. Prior to meta-analysis, the studies were evaluated for publication bias and heterogeneity. Pooled relative risk estimates (RR) and 95% confidence intervals (CIs) were calculated.

Results
Ten reports (six case–control and four cohort studies), published between 1998 and 2004, were identified. There was no evidence of an association between aspirin use and ovarian cancer risk either assuming a random-effects model (RR = 0.92, 95% CI 0.80, 1.06), or a fixed-effects model (RR = 0.93, 95% CI 0.81, 1.06). Similarly, we did not find evidence of an association between non-aspirin NSAID use and ovarian cancer, both on the basis of a random-effects model (RR = 0.86, 95% CI 0.68, 1.08), and on the basis of a fixed-effects model (RR = 0.88, 95% CI 0.76, 1.01). When the analyses were stratified into subgroups, there was no evidence that study design substantially influenced the estimate of effects. Furthermore, our analysis did not show decreasing risks with increasing frequency or duration of use, features often associated with causal relationships.

Conclusions
Our meta-analysis findings do not support that NSAID use plays a role in the chemoprevention of ovarian cancer. Future research should examine potential relationships between specific NSAIDs and ovarian cancer, taking into account the possible biases that may have affected this meta-analysis.

Introduction

Ovarian cancer remains the most lethal of the gynaecological cancers [1]. Although relatively uncommon, afflicting ~1 in 60 women in the USA, the high mortality rate makes this disease a major health concern. The high mortality rate arises from the lack of an effective screening approach [2] combined with inadequate therapeutic approaches for advanced disease [3]. Indeed, fewer than 25% of ovarian cancers are identified at an early curable stage. Strategies that focus on prevention may therefore provide the most rational approach for meaningful reductions in deaths attributable to ovarian carcinoma [4].

Two dominant hypotheses – the ovulation hypothesis [5, 6], which relates ovarian cancer risk to incessant ovulation, and the pituitary gonadotropin hypothesis [7], which implicates elevations in gonadotropin/oestrogen levels – have sought to explain the genesis of this disease, but epidemiological and biological observations do not fit entirely with either theory. Epidemiological evidence suggests that ovarian cancer may be related to chronic inflammatory processes. Ness and Cottreau proposed that inflammation of the ovarian epithelium is a pathophysiological contributor to the development of ovarian cancer [8]. Therefore, nonsteroidal anti-inflammatory drugs (NSAIDs) are potential agents for the chemoprevention of ovarian cancer.

Several observational epidemiological studies have examined the relation between NSAIDs and ovarian cancer. The findings from these studies are inconsistent. Some reported that the use of these drugs is inversely related to the risk of ovarian cancer, while others found no or positive associations. Thus, the effect of NSAID use on the risk of ovarian cancer remains to be determined.

Some recent review articles [9–11] have summarized the association between NSAID use and ovarian cancer risk. However, none of these articles has made a quantitative meta-analytic approach, and certainly none focused specifically on ovarian cancer. Therefore, we systematically identified case–control and cohort studies of the association between NSAID ingestion and ovarian cancer risk. We then performed a meta-analysis of these studies to evaluate the association, to compare the magnitude of any associations between aspirin and ovarian cancer with that between non-aspirin NSAIDs and ovarian cancer, and to examine associations with dose and with duration of NSAID use.

Materials and methods

Retrieval of published studies

To identify the studies of interest we conducted a computerized literature search. Sources included Medline (from 1966 to April 2004), Embase (from 1974 to April 2004) and Biosis (from 1993 to April 2004). Search terms included: ‘anti-inflammatory agents’ or ‘aspirin’ or ‘nonsteroidal anti-inflammatory drugs’ or ‘NSAIDs’ combined with ‘ovarian neoplasm’ or ‘ovarian cancer’ or ‘ovarian malignancy’. The title and abstract of studies identified in the computerized search were scanned to exclude any that were clearly irrelevant. The full texts of the remaining articles were read to determine whether they contained information on the topic of interest. The reference lists of articles with information on the topic were reviewed to identify citations to other studies of the same topic. Reference lists of review articles were also reviewed to check for completeness of the assembled list of relevant publications.

Inclusion and exclusion criteria

The studies considered in this meta-analysis were case–control or cohort studies that evaluated exposure to NSAIDs and ovarian cancer incidence and/or mortality.

Articles were excluded from the analyses for any one of the following reasons: (i) they did not include NSAID use as a risk factor for ovarian cancer; (ii) they did not provide an explicit description of NSAID exposure; (iii) there were insufficient published data for determining an estimate of relative risk or a confidence interval. In studies with multiple publications from the same population, only data from the most recent publication were included in the meta-analysis, with reference in the text to the older publication. Inclusion was not otherwise restricted by study size or language.

We did not assess the methodological quality of the primary studies, since quality scoring in meta-analysis of observational studies is controversial. Scores constructed in an *ad hoc* fashion may lack demonstrated validity, and results may not be associated with quality [12–14]. Instead, we performed subgroup analysis as widely recommended [14–16]. Hence, no study was rejected because of methodological characteristics or any subjective quality criteria.

We included in this meta-analysis studies reporting different measures of relative risk (odds ratio, incidence rate ratio, standardized incidence ratio). In practice, the three measures of effect yield very similar estimates of relative risk, since ovarian cancer is a rare occurrence.

Data extraction

Information from the studies was extracted by two independent reviewers (S.B. & K.F.) with the use of data abstraction forms. The following data were collected from each study, although some papers did not contain all the information: (i) publication data, first author’s last name, year of publication, and country of the population studied; (ii) study design; (iii) number of subjects; (iv) relative risks (RR) and 95% confidence intervals (95% CI); (v) case definition for ovarian cancer; (vi) definition of NSAID exposure; (vii) control for confounding factors by matching or adjustments. Inconsistencies were reviewed again until agreement was achieved.

In studies where more than one estimate of effect (RR) was presented, we chose the ‘most adjusted’ estimate; that was the estimate adjusted for the largest number of potential confounders.

Statistical analysis

Studies were grouped by the type of medicine (aspirin or non-aspirin NSAIDs). Two techniques were used to estimate the pooled relative risk estimates: the Mantel–Haenszel method [17] assuming a fixed-effects model, and the DerSimonian–Laird method [18] assuming a random-effects model. The fixed-effects model leads to valid inferences about the particular studies that have been assembled, and the random-effects model assumes that the particular study samples were drawn from a larger universe of possible studies and leads to inferences about all studies in the hypothetical population of studies. The random-effects approach often leads to wider confidence intervals. If heterogeneity is not present, the fixed-effects and the random-effects model provide similar results. When heterogeneity is found ($P < 0.05$), both models may be biased [19].

Publication bias was evaluated using the funnel graph, the Begg and Mazumdar adjusted rank correlation test [20] and the Egger regression asymmetry test [21]. The Begg and Mazumdar test is a statistical analogue of the visual funnel graph. It determines whether there is a significant correlation between the effect estimates and their variances. The absence of significant correlation suggests that the studies have been selected in an unbiased manner. The Egger regression asymmetry test tends to suggest the presence of a publication bias more frequently than the Begg approach. It detects funnel plot asymmetry by determining whether the intercept deviates significantly from zero in a regression of the standardized-effect estimates against their precision.

To evaluate whether the results of the studies were homogeneous, we used the Cochran's Q-test [22]. It is a c^2 test with degrees of freedom equal to the number of studies minus one, and tests the null hypothesis that the difference between the study estimates of relative risk is due to chance (the smaller the P-value, the less homogeneity present among study results). We also calculated the quantity I^2 [23], which describes the percentage variation across studies that is due to heterogeneity rather than chance. I^2 was calculated as $I^2 = 100\% \times (Q - df)/Q$, where Q is Cochran's statistic and df the degrees of freedom. Negative values of I^2 were put equal to zero, so that I^2 lies between 0% and 100%. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity [23].

Data were stratified into subgroups on the basis of study design. This was done to examine consistency across varying study designs with different potential biases. Homogeneity was assessed overall and within this stratification.

To assess any association between dose of NSAIDs and the risk of ovarian cancer, drug exposure was grouped as 'regular' and 'irregular'. 'Regular use' was the highest frequency, and 'irregular use' was the lowest frequency of drug use, as reported in the individual studies.

To assess any association between duration of NSAID use and the risk of ovarian cancer, we used the available data from studies, which dichotomized duration to <5 years and ≥ 5 years.

All P-values are two-tailed. For all tests, a probability level <0.05 was considered statistically significant.

Data reporting conforms to the guidelines proposed by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group [14].

STATA 6 software was used for the statistical analyses (STATA Corp., College Station, TX, USA).

Results

Search results

The primary computerized literature search identified 599 records. However, after screening the titles and abstracts, 573 were excluded because they were either animal studies or *in vitro* cell line experiments, review articles, or irrelevant to the current study. We retrieved 26 potentially relevant manuscripts for further review. The full text was read and the reference lists were checked carefully. Finally, we identified 17 studies examining the association between NSAID use and ovarian cancer [24–40].

Seven studies were excluded from the meta-analysis, because they evaluated the risk of ovarian cancer in patients with rheumatoid arthritis and did not provide an explicit description of NSAID exposure [24–27] or due to the rule for multiple publications from the same population [28, 29] or because they evaluated the use of analgesics as a risk factor for ovarian cancer, without differentiating between aspirin, acetaminophen and non-aspirin NSAIDs [30].

The remaining 10 studies were included in the meta-analysis [31–40]. Six out of 10 were case–control studies [35–40] and the remaining four were cohort studies [31–34]. There were no randomized trials. The number of cases ranged from 68 to 780 in the case–control studies, and from 34 to 333 in the cohort studies.

Nine out of 10 studies evaluated exposure to aspirin and ovarian cancer risk [31, 32, 34–40]. Six out of 10 evaluated exposure to non-aspirin NSAIDs and ovarian cancer risk [31, 33–35, 38, 40].

All studies [31–40] used newly diagnosed ovarian cancer as a case definition, and were controlled for potential confounding factors (at least for age), by matching or adjustments.

All case–control studies [35–40] had used noncancer controls. Among them, one study [38] had used two control groups, one cancer and one noncancer. However, we included in the meta-analysis the relative risk estimates derived from the analysis that had implicated the noncancer controls.

The majority of the studies were conducted in the USA [31, 34, 36–38, 40], but some were carried out in the UK [35] and Europe [32, 33, 39].

The publication dates of the studies included in the meta-analysis ranged between 1998 and 2004. Study designs, along with the estimated relative risks and 95% CIs, are shown in Table 1.

Meta-analysis of exposure to aspirin

Six case–control studies [35–40] and three cohort studies [31, 32, 34] evaluated exposure to aspirin and ovarian cancer risk.

The funnel plot did not have the expected funnel shape. The right corner of the pyramidal part of the funnel, which should contain small studies reporting positive or null results, was missing (Figure 1). The *P*-values for the Begg and Mazumdar test and Egger test were $P = 0.05$ and $P = 0.01$, respectively, both suggesting the existence of publication bias, a phenomenon in which studies with statistically significant results are more likely to be published compared with nonsignificant and null results. In contrast, the Cochran's *Q*-test had a *P*-value of 0.37 ($Q = 8.74$ on eight degrees of freedom) and the corresponding quantity I^2 was 8%, both indicating very little variability between studies that cannot be explained by chance (Table 2).

The association of aspirin use with ovarian cancer was not statistically significant assuming either a fixed-effects model (RR = 0.93, 95% CI 0.81, 1.06), or a random-effects model (RR = 0.92, 95% CI 0.80, 1.06) (Table 2).

After stratifying the data into subgroups, on the basis of study design, we found no association between aspirin use and ovarian cancer, either among case–control studies (random-effects model, RR = 0.83, 95% CI 0.65, 1.05), or among cohort studies (random-effects model, RR = 1.00, 95% CI 0.84, 1.20) (Table 2). Figure 2 graphs the RRs and 95% CIs from the individual studies and the pooled results.

To analyse any association between dose of aspirin and the risk of ovarian cancer, drug exposure was grouped as 'regular' and 'irregular'. 'Regular use' was the highest frequency, and 'irregular' was the lowest frequency of drug use, as reported in the individual studies. Three studies [31, 34, 37] contributed to this analysis. The calculated pooled RR estimates for both 'regular' and 'irregular' use of aspirin were not statistically significantly different than unity (Table 2), providing little evidence of a dose relationship between the frequency of aspirin use and risk of ovarian cancer.

To assess any association between duration of aspirin use and the risk of ovarian cancer, we used the available data from studies, which dichotomized to <5 years and ≥5 years. Once again, the calculated pooled RRs for short and prolonged duration of use were both compatible with 1.0 (Table 2), providing little evidence of an association between the duration of aspirin use and risk of ovarian cancer.

Meta-analysis of exposure to non-aspirin NSAIDs

Three case–control studies [35, 38, 40] and three cohort studies [31, 33, 34] evaluated exposure to non-aspirin NSAIDs and ovarian cancer risk.

This time, the funnel plot had the expected funnel shape (Figure 1). The *P*-values for the Begg and Mazumdar test and Egger test were $P = 1.00$ and $P = 0.73$, respectively, both suggesting a very low probability of publication bias. In contrast, the Cochran's *Q*-test had a *P*-value of 0.09 ($Q = 9.45$ on five degrees of freedom) and the quantity I^2 was 47%, both providing evidence of heterogeneity among the studies (Table 2).

The association of non-aspirin NSAID use with ovarian cancer was not statistically significant assuming either a fixed-effects model (RR = 0.88, 95% CI 0.76, 1.01), or a random-effects model (RR = 0.86, 95% CI 0.68, 1.08) (Table 2).

After stratifying the data into subgroups, on the basis of study design, we found no association between non-aspirin NSAIDs use and ovarian cancer, either among case–control studies (random-effects model, RR = 0.89, 95% CI 0.53, 1.49), or among cohort studies (random-effects model, RR = 0.84, 95% CI 0.66, 1.07) (Table 2). Figure 2 graphs the RRs and 95% CIs from the individual studies and the pooled results.

Four studies [31, 33–35] provided results on frequency of use of non-aspirin NSAIDs. The calculated pooled RR estimates for both 'regular' and 'irregular' use of non-aspirin NSAIDs were both compatible with unity (Table 2), providing no evidence of a dose effect.

None of the studies included in the meta-analysis provided adequate information to assess any association between duration of non-aspirin NSAIDs use and the risk of ovarian cancer.

Discussion

The current interest in aspirin and other NSAIDs as potential agents for the chemoprevention of ovarian cancer stems from the fact that many animal experiments

Table 1
Studies included in the meta-analysis

Study	Study location	Study design	All subjects	OC cases	Aspirin use		NA-NSAID use		Control for potential confounders*	Source of exposure data
					RR	(95% CI)	RR	(95% CI)		
Lacey *et al*. 2004 [31]†	USA	Cohort	31364	116	0.86	(0.52, 1.4)	1.0	(0.60, 1.8)	1,2,3,4,5,6	Questionnaire
Friis *et al*. 2003 [32]	Denmark	Cohort	29470	34	1.1	(0.7, 1.5)	–	–	1	Database
Sorensen *et al*. 2003 [33]	Denmark	Cohort	172057	130	–	–	0.9	(0.7, 1.0)	1	Database
Fairfield *et al*. 2002 [34]	USA	Cohort	76821	333	1.0	(0.8, 1.25)	0.60	(0.38, 0.95)	1,3,7,8,9,10,11	Questionnaire
Meier *et al*. 2002 [35]	UK	C-C	2360	483	0.1	(0.02, 1.0)	1.1	(0.7, 1.8)	7,9,12	Database
Akhmedkhanov *et al*. 2001 [36]	USA	C-C	748	68	0.6	(0.26, 1.38)	–	–	3,8,13,14	Questionnaire
Moysich *et al*. 2001 [37]	USA	C-C	1641	547	1.0	(0.73, 1.39)	–	–	1,4,8,11,15,16	Questionnaire
Rosenberg *et al*. 2000 [38]	USA	C-C	3350	780	0.8	(0.5, 1.2)	0.5	(0.3, 0.9)	1	Interview
Tavani *et al*. 2000 [39]	Italy	C-C	1647	749	0.93	(0.53, 1.62)	–	–	1,3,7,8,17,18	Interview
Cramer *et al*. 1998 [40]	USA	C-C	1086	563	0.78	(0.53, 1.15)	1.20	(0.74, 1.95)	1,3,8,12,17,19,20	Interview

*OC, Ovarian cancer; NA-NSAIDs, non-aspirin nonsteroidal anti-inflammatory drugs; RR, relative risk; CI, confidence intervals. *1, Age; 2, ethnicity; 3, oral contraceptive use; 4, family history of ovarian cancer; 5, menopausal status; 6, duration of oestrogen use; 7, body mass index; 8, parity; 9, smoking; 10, postmenopausal hormone use; 11, tubal ligation history; 12, acetaminophen use; 13, age at menarche; 14, first degree family history of breast cancer before age 50; 15, age at first birth; 16, presence of irregular menses; 17, education; 18, age at menopause; 19, religion; 20, menstrual pain, headache, arthritic pain. †Numbers in parentheses, reference citation.*

and human epidemiological studies link aspirin and other NSAIDs with beneficial effects in various cancers, including breast, oesophageal, colorectal and prostate cancer. Recent meta-analyses have supported the idea that the overall relative risk of breast [41], gastric [42], oesophageal [43] and prostate cancer [44] is reduced in people taking aspirin and other NSAIDs.

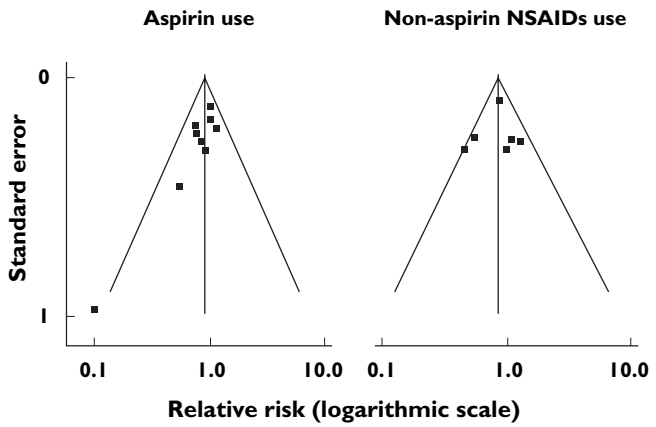

Figure 1
Funnel plots of the relative risk of developing ovarian cancer, by the standard error, for all studies (■) included in the meta-analysis. Relative risks are displayed on a logarithmic scale. For aspirin use: $P = 0.05$ for the Begg–Mazumdar test; $P = 0.01$ for the Egger test. For non-aspirin NSAIDs use: $P = 1.00$ for the Begg–Mazumdar test; $P = 0.73$ for the Egger test

To the best of our knowledge, this is the first meta-analysis of published studies to evaluate specifically the association between NSAID use and ovarian cancer risk. According to the findings of our meta-analysis, NSAID use does not appear to affect the risk of developing ovarian cancer. Furthermore, our results did not show decreasing risks with increasing frequency or duration of use, features often associated with causal relationships.

Our results are in agreement with cohort studies of women with rheumatoid arthritis, who chronically use NSAIDs. In a Swedish cohort [24] of nearly 8000 women, the standardized incidence ratio was 0.96, based on 30 cases of ovarian cancer. In a Danish cohort [25] of nearly 14 000 women, there were 50 incident cases, corresponding to a relative risk of 1.0. In a Canadian cohort [26] of women with rheumatoid arthritis, the standardized incidence ratio was 0.89, based on five cases. Similarly, in the Rochester rheumatoid arthritis cohort [27], there was one case of ovarian cancer on two expected.

When meta-analysis of observational data is performed, consideration of study bias is critical [14].

Table 2
Meta-analysis results

	No. of studies	Fixed-effects model RR	(95% CI)	Random-effects model RR	(95% CI)	Tests of homogeneity Q-value (df)	*P*-value	I^2	Tests of publication bias Begg's P-value	Egger's P-value
Aspirin										
All studies	9	0.93	(0.81, 1.06)	0.92	(0.80, 1.06)	8.74 (8)	0.37	8%	0.05	0.01
C-C studies	6	0.85	(0.70, 1.03)	0.83	(0.65, 1.05)	6.61 (5)	0.25	24%	0.13	0.02
Cohort studies	3	1.00	(0.84, 1.20)	1.00	(0.84, 1.20)	0.60 (2)	0.74	0%	1.00	0.81
'Regular use'	3	0.89	(0.65, 1.20)	0.89	(0.65, 1.20)	1.00 (2)	0.61	0%	0.30	0.17
'Irregular use'	3	1.09	(0.87, 1.35)	1.09	(0.87, 1.35)	0.08 (2)	0.96	0%	1.00	0.50
Duration = 5 years	4	0.73	(0.48, 1.12)	0.73	(0.48, 1.12)	2.38 (3)	0.50	0%	1.00	0.92
Duration <5 years	4	0.89	(0.69, 1.15)	0.89	(0.69, 1.15)	1.24 (3)	0.74	0%	0.31	0.49
NA-NSAIDs										
All studies	6	0.88	(0.76, 1.01)	0.86	(0.68, 1.08)	9.45 (5)	0.09	47%	1.00	0.73
C-C studies	3	0.91	(0.69, 1.22)	0.89	(0.53, 1.49)	6.44 (2)	0.04	69%	1.00	0.17
Cohort studies	3	0.87	(0.74, 1.01)	0.84	(0.66, 1.07)	2.91 (2)	0.23	31%	1.00	0.71
'Regular use'	4	0.88	(0.67, 1.15)	0.88	(0.63, 1.23)	4.35 (3)	0.23	31%	0.73	1.00
'Irregular use'	4	0.92	(0.78, 1.10)	0.83	(0.59, 1.15)	6.66 (3)	0.08	55%	1.00	0.28
Duration = 5 years	–	–	–	–	–		–	–	–	–
Duration <5 years	–	–	–	–	–		–	–	–	–

RR, Relative risk; CI, confidence interval; NA-NSAIDs, non-aspirin nonsteroidal anti-inflammatory drugs; df, degrees of freedom.

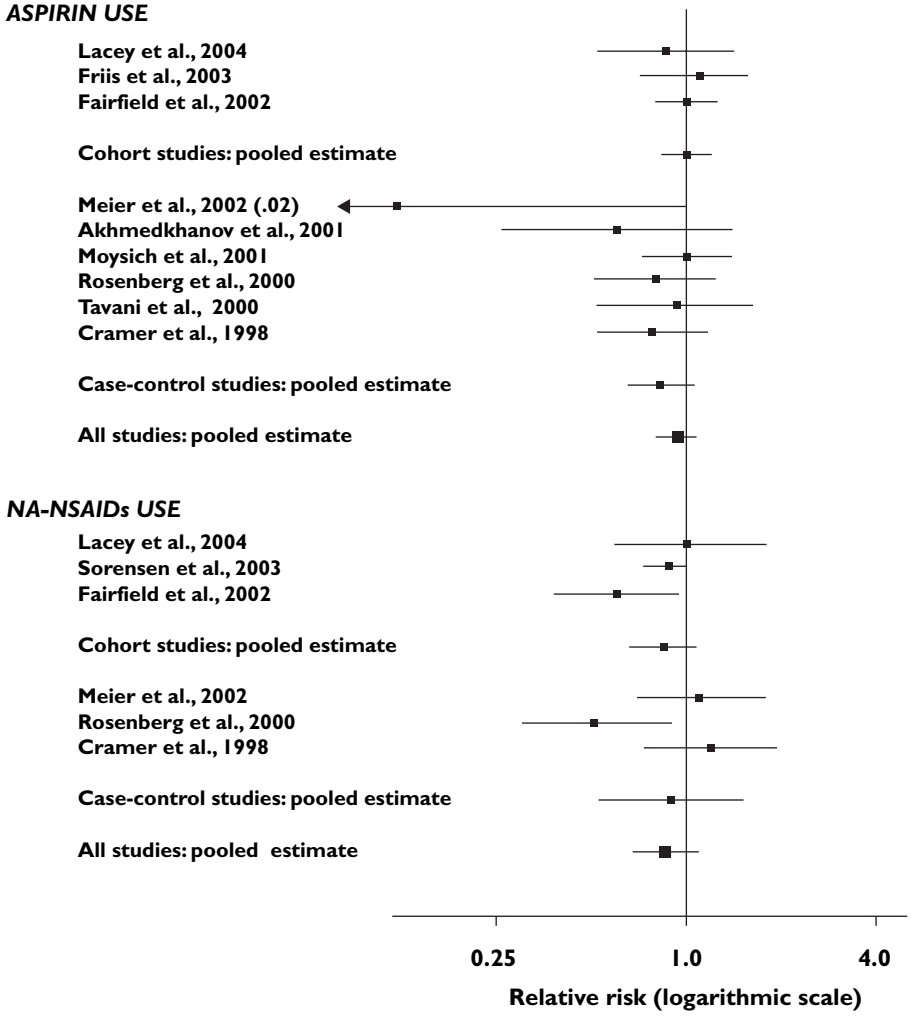

Figure 2
Analysis of studies, denoted by first author and publication year, which examined ovarian cancer and its association with NSAID use. The relative risk and 95% CI for each study are displayed on a logarithmic scale. Pooled estimates are from a random-effects model

Existence of a bias in favour of publication of statistically significant results is well documented in the literature [45–47]. The publication bias detected in the meta-analysis of exposure to aspirin implies that the statistically nonsignificant 8% reduction of risk shown (RR = 0.92) is overestimated. It was also shown that the right corner of the pyramidal part of the funnel for aspirin, which should contain studies reporting positive or null results, was missing (Figure 1). It indicates that studies for which the direction of estimate was against expectations (i.e. more than 1.0) may have been less likely to be published than those which showed a trend in the direction expected. This fact is compatible with the overall conclusion that aspirin use is not correlated to ovarian cancer risk.

Nevertheless, several limitations should be considered in interpreting the results of this meta-analysis. First, our search was restricted to studies published in indexed journals. We did not search for unpublished studies or for original data. However, we did not impose any exclusion criteria with regard to language, place of publication or quality.

Second, the included studies were different in terms of study design and definitions of drug exposure. We tried to explore sources of heterogeneity conducting several subgroup analyses. However, the summary effect estimates are based on sparse and heterogeneous data. Similarly, for the non-aspirin NSAIDs, all drugs have been regarded as being the same. Pharmacologically, this is not correct in that the drugs are different in terms of kinetics and dynamics, and may therefore have different effects on risk.

Third, the method used to elicit the exposure differs among the individual studies. Most studies [31, 34, 36–40] used personal interviews or self-administered questionnaires that rely on the subject's ability to recall, which was repeatedly shown to be relatively poor for nonrepetitive NSAID use [48]. Fewer studies [32, 33, 35] used automated databases that provide detailed information on dates of use and types of drugs used.

This information is equally good for cases and controls irrespective of the event of interest, since it was recorded prospectively. However, studies that used prescription databases lacked information on over-the-counter use, and were based on the assumption that the amount of NSAIDs dispensed is a good approximation of actual consumption. This may not be true, especially for non-aspirin NSAIDs that are frequently prescribed to be taken only when needed.

Fourth, observational studies lack the experimental random allocation of the intervention necessary to test exposure-outcome hypotheses optimally. Thus, results may have been confounded by several factors, given that each one of the studies included in our meta-analysis controlled for somewhat different confounding factors (Table 1). None of the individual studies adjusted for some factors that may affect the use of these drugs, such as the motivation for NSAID use [49, 50]. For example, aspirin is also used in the primary and secondary prevention of coronary heart disease. We cannot totally exclude the possibility that earlier mortality among aspirin users (e.g. from heart disease) may preclude diagnosis of ovarian cancer and therefore produce a beneficial effect.

Fifth, dose relationship was evaluated on the basis of regular and irregular intake, which are not very precise and may not by themselves indicate the lack of dose dependency. Therefore, our results should be interpreted with caution.

Several laboratory studies have tried to investigate the link between NSAIDs and ovarian cancer and explore the potential underlying mechanisms. At present, investigation relies on ovarian cancer cell lines and cultures of normal ovarian epithelium [51]. The studies by Rodriguez-Burford *et al.* [52] demonstrated that acetylsalicylic acid and a COX-2 inhibitor (NS-398) can decrease the growth of fully transformed epithelial ovarian cancer cells. The COX-2 agent both decreased cell proliferation in established cell lines and induced apoptosis in freshly isolated ovarian cancer cells. However, concentrations far above the therapeutic range and well above the maximal tolerated dose were required to demonstrate anti-proliferative effects *in vitro*. This is compatible with the observation that human epithelial ovarian cancer cells appear to express COX-1 and COX-2 at very low levels [52, 53]. In contrast, bowel cancer cells are very sensitive to the effects of NSAIDs, probably as a consequence of overexpression of COX-2, and dependent on COX-2 function for growth and survival [54–57].

Thus, the observations that very high concentrations of NSAIDs are required to decrease the proliferation of ovarian cancer cell lines and that ovarian cancer cells express very low levels of COX-1 and COX-2 [52, 53] are compatible with the findings of our meta-analysis of observational studies.

In conclusion, the findings of our meta-analysis do not support that NSAID use plays a role in the chemoprevention of ovarian neoplasia. However, whilst the data provide no evidence for a beneficial effect, reductions in risk, which would be clinically important, cannot be excluded. Therefore, future research should examine potential relationships between specific NSAIDs and ovarian cancer risk, over extended periods of time, with examination of subgroups that may benefit most from anti-inflammatory effects. Because long-term NSAID use may occasionally result in serious gastrointestinal bleeding and haemorrhagic stroke, the risk–benefit balance of long-term NSAID use should also be assessed.

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